FDA Considers Restricting or Banning Laparoscopic Morcellation

By Vicki Brower

The U.S. Food and Drug Administration is considering restricting or banning morcellation in minimally invasive hysterectomies and myomectomies (removal of fibroids) because of new reports of higher incidence of undiagnosed sarcoma in women undergoing these procedures. Research now links morcellation to the spread, or upstaging, of undetectable gynecological cancers. In July, FDA convened a 2-day Obstetrics and Gynecology Devices Advisory Committee meeting to discuss risks and benefits of morcellation and to determine ways to reduce risk of upstaging cancers.

In December 2013, after receiving the first report of an upstaged cancer due to morcellation, FDA sent out a safety communication to discourage morcellation in laparoscopic gynecologic surgeries. Women whose cancers upstaged after morcellation live a median of 11.5 months after the procedure. About 50,000 U.S. women per year undergo morcellation. Other risks include visceral and vascular injuries, Craig J. Sobolewski, M.D., assistant professor at Duke University in Durham, N.C., said at the meeting. Owing to the report and the FDA warning, several U.S. medical centers have stopped using laparoscopic power morcellation (LPM), and Johnson & Johnson's Ethicon device subsidiary has stopped marketing its morcellator.

Previously thought to be much rarer, uterine sarcomas, and especially leiomyosarcomas, are lethal and virtually impossible to detect. In April, FDA increased the estimate of sarcoma risk for women undergoing hysterectomy or myomectomy for presumed fibroids from between 1 in 500 and 1 in 10,000 to about 1 in 352 for unsuspected uterine sarcomas, and 1 in 498 for leiomyosarcomas. The most recent study, by Jason Wright, M.D., chief of gynecologic oncology at Columbia University in New York, found that cancer risk in women undergoing hysterectomy for symptomatic fibroids is 1 in 370 (JAMA online, July 22, 2014). The study also detected other malignancies and precancerous abnormalities.

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“Although morcellators [surgical instruments that assist in laparoscopic surgery] have been in use since 1993, few studies have described the prevalence of unexpected pathology at the time of hysterectomy,” the authors wrote. “Prevalence information is the first step in determining the risk of spreading cancer with morcellation,” they noted.

Patients considering morcellation should be adequately counseled about the prevalence of cancerous and precancerous lesions, Wright said. After a period of public comment on the July meeting and the participation of surgeons and other experts, patients, and their families, FDA will issue its decision about whether to restrict or ban morcellation.

20 Years of Morcellation
LPM uses a morcellator to slice tissue into small pieces, enabling surgeons to remove the uterus and fragments of large fibroids without making large incisions. But LPM can lead to complications. The procedure can spread cells and tissue fragments throughout the peritoneal cavity. If benign, these cells can grow and cause adhesions, causing pain and dysfunction. If cancerous, they can lead to inaccurate
diagnosis and staging, and spread cancer. Whether they are cancerous, is determined only after surgery.

In 25%–64% of cases, morcellation upstages early-stage disease to stage III or IV, according to FDA. The 5-year survival rate is 60% for patients with stage I leiomyosarcoma, 22% for those with stage III, and 15% for those with stage IV disease.

Although surgeons have used morcellators in minimally invasive gynecological surgery for about 20 years, FDA received the first adverse-event report in December 2013. Amy Reed, M.D., an attending anesthesiologist at Boston’s Beth Israel Deaconess Medical Center, had an undetectable, or hidden, cancer that LPM upstaged. She and her husband, Hooman Noorchashm, M.D., a cardiothoracic surgeon at Boston’s Brigham and Women’s Hospital, spoke with the media and lobbied FDA to ban LPM. To date, they have identified about 100 women with hidden, morcellated uterine cancers that LPM upstaged.

“Hidden sarcomas are lethally harmful, and increased harm from them is completely avoidable. The evidence of harm is overwhelming and the ethical violation is undeniable,” Noorchashm said.

Noorchashm, Reed, and other patients and families of patients testified about their experiences and urged FDA to ban morcellation until and unless it can be done safely. Others recommended mitigating morcellation risks short of pulling the devices from the market. Many surgeons that practice minimally invasive surgery (MIS) maintain that many more women will be at risk for complications of open surgery if morcellation is banned.

Many questions remained after presentations by FDA, surgeons, patients, and professional medical societies. Ultimately, FDA does not want to inhibit innovation, it said, but questions whether current morcellation technology and imaging capability can reduce the risk of unknowingly spreading cancer.

Polarized Views

The controversy reflects a disagreement between champions of MIS, who take a public-health perspective of doing what’s best for most patients, and those who believe that the risk of spreading cancer is unacceptable even if it is only in relatively few patients. Panel member Mark Talamini, M.D., chairman of surgery at Stony Brook University School of Medicine in Stony Brook, N.Y., summed up the debate: “The risk of sarcoma in women may be very small, but if one has cancer, the risk of harm with morcellation is huge.”

Others, however, advocate for continued use of morcellation with risk mitigation strategies. Panel member Keith Isaacson, M.D., medical director of the Newton–Wellesley Hospital Center for Minimally Invasive Gynecological Surgery in Newton, Mass., believes that reverting to open hysterectomies will expose thousands of women to more harm, including blood clots, blood loss, infection, and longer recovery time. Such advocates view the issue as an either/or choice: either MIS with morcellation or open surgery. But others say that excellent alternatives to MIS and morcellation are available, such as vaginal hysterectomy and minilaparotomy.

For women, in whom sarcomas are not as rare as previously thought, and for which diagnosis before surgery is not possible, Reed, Noorchashm, other patients and their families, and some experts view the risk as unacceptable.

Patients are angry that no one told them that their surgery would involve morcellation—or that the procedure carried risks. Some patients requested open surgery because of fear of cancer, but doctors would not perform such surgery, saying that risks of open hysterectomy were much greater than the chance of finding cancer. The issue of upstaging cancer if found was also not disclosed.

“I had been assured by my surgeon that I did not have cancer because of his certainty that my disease was benign, and he actually declined to perform an open hysterectomy although I requested it,” said Antonio Pizzaro, M.D., a gynecologic surgeon in private practice in Shreveport, La., who did not participate in the meeting. “FDA’s new assessment has unequivocally—if unwittingly—called into question every nonsurgical treatment for fibroids,” he said.

Isaacson and other surgeons who practice MIS object to a ban, maintaining that open hysterectomies—the only other option, they contend—are risky.

“If we accept the increased risks, we must now consider all fibroids as cancer and not morcellate,” said Antonio Pizzaro, M.D., a gynecologic surgeon in private practice in Shreveport, La., who did not participate in the meeting. “FDA’s new assessment has unequivocally—if unwittingly—called into question every nonsurgical treatment for fibroids,” he said.

“While we’ve always assumed fibroids are benign,” said Joseph Ranieri, M.D., associate professor of women’s health and reproductive science at New York’s Mount Sinai School of Medicine. “If we now assume they all might be malignant, where are we?”

Whereas Pizzaro and Ranieri believe abandoning MIS and morcellation to be extreme, Col. Craig Shriver, M.D., at Walter Reed Army Medical Center in Bethesda, Md., and others are more comfortable that “we must assume the worst and treat as such”—without morcellation.
Beyond Counting: New Way To Use Circulating Tumor Cells

By Anna Azvolinsky

In 2007, researchers at Boston’s Massachusetts General Hospital (MGH) Cancer Center showed that a microfluidic device, the CTC-Chip, could separate and count rare circulating tumor cells (CTCs) in whole-blood samples (Nature 2007;450:1235–9). Last year, the team developed the CTC-iChip, a refined version of its predecessor, and confirmed its utility in catching viable CTCs. This device can profile individual CTCs—including their DNA mutations and RNA and protein expression—at the molecular level (Sci. Transl. Med. 2013;5:179ra47; doi:10.1126/scitranslmed.3006516).

Going further, the teams recently showed that CTCs captured with CTC-iChip could be used to establish individual patient–based cell lines and xenograft models (Science 2014;345:216–20; doi:10.1126/science.1253533). These cell lines can test for drug sensitivity, which researchers hope will facilitate individualized cancer treatment options. These findings took place in the MGH laboratories of Daniel Haber, M.D., Ph.D., Shyamala Maheswaran, Ph.D., and Mehmet Toner, Ph.D.

The goal of culturing these cells ex vivo, according to Haber, is to enable functional analysis. Genetic testing for mutations often, but not always, is associated with drug response, he said.

“Testing whether a drug really works in killing a cancer cell with a given mutation [would be] helpful. This becomes even more relevant when multiple mutations are present [in CTCs], each of which could be driving the cancer,” Haber said.

CTCs are found in minute quantities in the blood of cancer patients, shed from either the primary or metastatic tumor. Research has statistically correlated CTCs with both patient survival and disease progression for certain cancers. Because a simple blood draw is appealing to both patient and clinician, researchers and companies have tried to detect and characterize CTCs in lieu of invasively taking a tumor sample.

Still, most research on CTCs is confined to preclinical and academic studies. So far, the U.S. Food and Drug Administration has approved only one CTC detection tool: CellSearch. Made by Johnson & Johnson’s Janssen Diagnostics, CellSearch counts CTCs—those of an epithelial origin that express the surface epithelia cell adhesion molecule—in blood samples from breast, prostate, and colorectal cancer patients.

Agnostic Approach

Unlike CellSearch, the new CTC-iChip does not detect CTC cell surface markers. These biomarkers can vary among cancers and even change in the same cancer patient...